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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,466	10/13/2005	Etienne Pays	VANM290.002APC	3679

20995 7590 11/04/2008

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
11/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,466	PAYS ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,13-31* is/are pending in the application.

4a) Of the above claim(s) *3-9,13-20 and 22-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8,10,21,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 5/3/04 is made. Claims 1, 3, 8, 10, 21, 30 and 31 are currently under examination.

Claims 3-9, 13-20 and 22-29 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112-2nd paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 3, 8, 10, 21, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it recites “or a fragment thereof that inhibits trypanosome infection”. Accordingly, it is unclear what percent identity this fragment is required to possess. It appears that it may be less than 95%. Additionally, this fragment encompasses sequences outside of SEQ ID NO: 1, e.g., fragments from the 5% of the sequence which varies from SEQ ID NO: 1 are included. Accordingly, the metes and bounds of the claim cannot be understood. Clarification and correction is requested.

Claim 3 is vague and idefinite due to the term ‘trypanolytically” active fragment. It is unclear that this is an art accepted word. Additionally, is this an enzyme? How is the

fragment 'trypanolytically' active. The meaning of the word cannot be understood. What is a 'trypanolytically active' fragment? Claim 3 recites the limitation "trypanolytically active fragment" in line 2. There is insufficient antecedent basis for this limitation in the claim as claim 1 recites fragments which inhibit trypanosome infection which do not appear to be the same thing as 'trypanolytically active'.

Claim Rejections - 35 USC § 112-Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3, 8, 10, 21, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for " a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and an isolated polypeptide comprising SEQ ID NO: 1 (and the specific fragments recited in claim 3)", **does not** reasonably provide enablement for pharmaceutical compositions comprising a polypeptide having 95% greater identity to SEQ ID NO: 1 or any fragment thereof that inhibits any trypanosome infection, any composition comprising or for any method of *prevention or amelioration* of infection by *any* species of Trypanosmoma through the administration of the polypeptide comprising SEQ ID NO: 1 or the fragments recited in claims 1 and 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

First, the breadth of the instant claims is drawn to polypeptides which are not specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions.

The instant claims are drawn to proteins comprising a sequence with any given percent similarity to a protein, e.g., homolog. Selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss

of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the native, and be ineffective in treating or preventing diseases or conditions or for detection. Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a dingle amino acid difference may account for markedly different biological activities. The prior art also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study.

The fragment of a sequence having greater than 95% identity to SEQ ID NO:! encompasses sequences outside of SEQ ID NO: 1, e.g., fragments comprising portions from the 5% of the sequence which varies from SEQ ID NO: 1 are included.

The specification is also not enabled for pharmaceuticals, vaccines or methods of using the full-length proteins set forth in SEQ ID Nos: 1 (or the fragments thereof included in the claims) to prevent, inhibit or ameliorate any infection caused by any species of Trypanosoma. The instant specification provides neither *in vitro* or *in vivo* results of treating or protecting against diseases caused by these organisms. In such an unpredictable art, specific evidences would need to be present in order to enable such a scope of invention. The specification is not enabled for use of variant polypeptide sequences or fragments any of the claimed treatment methods or as a diagnostic. The location of protective epitopes have not been identified. Often times it takes more than one epitope to provide a protective effect. As stated above, selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. The prior art (see Tytler et al Mol. and Biochem. Parasitolog. 69 (1995): 9-17, specifically page 16) has taught that chemotherapy has been the standard treatment of African trypanosomes because they evade the immune system of the mammalian hosts

by changing their variant surface glycoproteins which make up the surface coat of the bloodstream forms. Accordingly, the use of treatment other than chemotherapeutic agents, such as protein, has been highly unpredictable. It would take undue experimentation for one of skill in the art to use any of the claimed fragments, homologs or even the full-length polypeptide to *prevent,* much less treat, disease caused by any trypanosomes. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicant's arguments:

Applicants argue that any desired fragment of SEQ ID NO: 1 can be produced using methods well known to one of skill in the art and evaluated for trypanolytic activity. The argue that although the generation of mutants and fragments and testing them for trypanolytic activity would be tedious, it would not be undue. Applicant argue that the

method steps recited in the specification enable treatemen of ameliorating and/or preventing a Trypanosoma infection. These arguments have been fully and carefully considered but are not deemed persuasive. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

As stated in the rejection outlined above, itt would take undue experimentation for one of skill in the art to use any of the claimed fragments, homologs or even the full-length polypeptide to *prevent or ameliorate,* much less treat, disease caused by any trypanosomes. The fragment of a sequence having greater than 95% identity to SEQ ID NO: 1 encompasses sequences outside of SEQ ID NO: 1, e.g., fragments comprising portions from the 5% of the sequence which varies from SEQ ID NO: 1 are included. The instant specification provides neither *in vitro* or *in vivo* results of treating or protecting against diseases caused by these organisms. In such an unpredictable art, specific evidences would need to be present in order to enable such a scope of

invention. The specification is not enabled for use of variant polypeptide sequences or fragments any of the claimed treatment methods or as a diagnostic. The location of protective epitopes have not been identified. Often times it takes more than one epitope to provide a protective effect. As stated above, selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue.

When considering a microbial/parasitic antigen as a vaccine candidate, three major considerations must be raised (1) the antigen must be conserved among strains of the species whose disease one wishes to prevent; (2) it must generate protective antibody such that the antibody to the antigen prevents disease; and (3) it msut be a good immunogen such that protective antibodies are elicited in the population at risk and that these antibodies persist for sufficient time to provide protection throughout the risk period. Even when an antigen meets these three considerations, further testing often indicates that the antigen will not be effective as a vaccine. For example, Murphy et al. Pediatr. Infect. Dis. J. 1989. 8: S66-S68, teach that P6 is an important vaccine candidate based on these considerations, but Yamanaka et al (J. Pediatrics. 1993. 122(2): 212-218) later demonstrated that the population at most risk did recognize P6 as an antigen. The instant specification fails to demonstrate that the claimed antigen meets any of the three considerations known in the art to be important when

considering an antigen as a vaccine candidate. Without specific guidance from the specification, it would take undue experimentation for those skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112-Written Description

5. Claims 1, 3, 8, 10, 21, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims drawn to any homolog.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome.....

and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of allelic variants is made in the specification. This is insufficient to support the generic claims as provided by the

Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore, the full breadth of the claims does not meet the written description provisions of 35 USC 112, first paragraph.

Response to Applicant's arguments:

The fragment of a sequence having greater than 95% identity to SEQ ID NO: 1 encompasses sequences outside of SEQ ID NO: 1, e.g., fragments comprising portions from the 5% of the sequence which varies from SEQ ID NO: 1 are included. These variant fragments are not provided written description in the instant specification.

Claim Rejections - 35 USC § 102- Rejections withdrawn

6. The former claim rejections as anticipated by Duchateau et al (J.Lipid Research. 42: 62—630. 2001) and Tytler et al (Molec. And Biochem. Parasitology. 1995. pages 9-17)) have been obviated by Applicant's arguments and amendments to the claims.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

10/30/08